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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/701,947	12/05/2000	Elliot Altman	235.00010101	9854

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EXAMINER	
LIU, SAMUEL W	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 11/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/701,947	ALTMAN, ELLIOT	
	Examiner	Art Unit	
	Samuel W Liu	1653	

-- The MAILING DATE of this communication app ars on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 61-128* is/are pending in the application.

4a) Of the above claim(s) *1, 61-88, 98-103 and 106-119* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *89-97,104,105 and 120-128* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' response filed 22 August 2003, which adds claims 123-128 and amends claims 89-97, 104-105 and 120-122 has been entered. Note that claims 1 and 61-128 are pending; of these claims 1, 61-88, 98-103 and 106-119 are withdrawn from further consideration as being drawn to a non-elected invention, and claims 2-60 are cancelled previously by the applicants' amendment filed 7 May 2001. The pending claims 89-97, 104-105 and 120-128 are examined in this Office action; the followings are or remain applicable to the claims.

Please note that grounds of objection and/or rejection not explicitly restated and/or set forth below are withdrawn.

The rejections under 35 USC 102 are withdrawn because the applicants' amendment to the claims obviates the rejections. Applicant's amendment necessitated the following new ground of rejection.

Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 89, 91, 104-105 and 120 are rejected under 35 U.S.C. 103(a) as being obvious over Anderson, D. et al. (US Pat. No. 6562617) taken with Vanhoof G. et al. (*FASEB J.* (1995) 9, 736-744).

Anderson et al. teach N- and/or C- fusion of a bioactive polypeptide to the stabilizing moiety/moieties which render the fused protein proteolytically stable (see abstract and column 39, lines 21-45), as applied to claims 89 and 105 and 120 of the instant application. Note that Anderson et al. fusion encompasses dual N- and C-terminal fusion partners (see abstract).

Anderson et al. do not explicitly teach characteristics of the stabilizing moieties.

Vanhoof et al. teach (i) Xaa-Pro moiety attached to N-terminus of bioactive peptide (indicated as "Y") against N-terminal proteolysis (see Table 5) and (ii) –Pro-Pro moiety conjugated to C-terminus of the bioactive peptide to protect the peptide from proteolytic degradation (see Table 5); thereby the above mentioned moieties act as the stabilizing groups for the fused protein, as applied to claims 89, 91, 104-105 and 120 of the current application.

It would have been obvious for the ordinary skilled artisan to combine the above references to successfully arrive at the claimed invention because Anderson et al. teach importance of N- and C-terminal fusions on increasing the interest polypeptide stability, and Vanhoof et al. teach the stabilizing group is proline-rich moiety.

When combine, there would have been the following noticeable advantages: (i) the fusion partner is a stability sequence to confer stability to the subject polypeptide, particularly proteolytic stability, as taught by Anderson et al. (see column 39, lines 21-23 and lines 40-45), and (ii) N- and/or C-termini "capped" with Pro-moieties render the subject protein resistant in a high degree to specific protease hydrolysis (see Table 5) or to *any mammalian* proteolytic enzyme (see abstract), as taught by Vanhoof et al.; Thus, the skilled artisan would have combined the above references to engineer the fusion construct comprising the Pro-moieties as N- and C- terminal stabilizing groups including the cleavage sites between the stabilizing

partners and the fused protein, in order to improve proteolytic stability of the interest protein which is susceptible to proteases action so as to achieve high yield of the engineered product.

Given the above motivation, one of ordinary skill in the art would have combined the above teachings to make and use the bioactive polypeptide fusion that comprises the stabilizing partners, e.g., Pro-rich moieties, which are of protease-resistance. Therefore, the claimed invention was *prima facie* obvious to make and use the invention at the time it was made.

Claims 89-90, 104-105 and 121-128 are rejected under 35 U.S.C. 103(a) as being obvious over Anderson, D. et al. (US Pat. No. 6562617) taken with Plaxco, K. W. et al. (*Curr. Opin. Stru. Biol.* (1998) 8, 80-85), Wood, T. K. (US Pat. No. 6630197), Ni, J, et al. (US Pat. No. 6566498) and Sachdev, D. et al. (*Prot. Exp. Purif.* (1998) 12, 122-132).

Anderson et al. teach N- and/or C- fusion of a bioactive polypeptide to the stabilizing moiety/moieties which render the fused protein proteolytically stable (see abstract and column 39, lines 21-45), as applied to claims 89-90, 104-105 and 121 of the instant application. Note that Anderson et al. fusion encompasses dual N- and C-terminal fusion partners (see abstract).

Anderson et al. do not explicitly teach that the stabilizing moieties are small stable protein.

Plaxco et al. teach four-helix bundle proteins, e.g., engineered Rop protein possesses extremely high resistance to proteolysis (i.e., high stability) as well as extremely high solubility (see page 81, the right column, the first paragraph), as applied to the application claims 90, 92-95 and 121-122. Wood et al. teach maltose-binding protein fusion to antimicrobial peptide, as

applied to claims 96-97 and 123-128. Ni et al. teach maltose-binding protein, which is a four-helix bundle protein, fusion to a interest protein increases stability of the fused protein thereof (see column 47, line 60 to column 48, line 4), as applied to the application claims 90, 92-94 and 122. Sachdev et al. teach a linker containing cleavage site (see Figure 1 and page 128), as applied to claims 104-105 of the current application.

It would have been obvious for the ordinary skilled artisan to combine the above references to successfully arrive at the claimed invention because (a) Anderson et al. teach importance of N- and C-terminal fusions on increasing the interest polypeptide stability, and (b) Plaxco et al. together with Ni et al., Wood et al. and Sachdev et al. teach that small protein characterized as four-helix bundle which acts as stabilizing moiety; and when fused with the interest protein, it stabilizes the protein thereof.

Furthermore, combination of the above reference teachings would have offered the following obvious advantages: (i) the fusion partner is a stability sequence to confer stability to the subject polypeptide, particularly proteolytic stability, as taught by Anderson et al. (see column 39, lines 21-23 and lines 40-45); (ii) when fusion with four-helix bundle protein, e.g., maltose-binding protein (MBP), not only increases stability of the fused subject protein but also facilitates the subject protein refolding *in vitro* (see page 130, the left column, the second paragraph) in addition to great enhancement of solubility of the protein thereof (see abstract), as taught by Sachdev et al.; and (iii) since the engineered four-bundle helix protein rapidly folds and has extremely high recovery rate upon recombinant production, as taught by Plaxco et al. (see page 81, the right column, and page 83, the right column, the last paragraph), the fusion of bioactive protein to the stabilizing group, i.e., the four-bundle helix protein, would be a big plus

for high yield production of recombinant protein in addition to enhancement of stability thereof. Thus, the skilled artisan would have combined the above references to engineer the fusion construct comprising the four helix bundle proteins, as N- and C- terminal stabilizing groups including the cleavage sites between the stabilizing partners and the fused protein, in order to improve stability and solubility as well as yield of the engineered product.

Would have been motivated by the above teachings and advantages, one of ordinary skill in the art would have combined the above teachings to make and use the bioactive polypeptide fusion that comprises the stabilizing partners, e.g., the small stable proteins featuring the four-helix bundle or Pro-rich moieties, which are of protease-resistance and high solubility. Therefore, the claimed invention (claims 89-90, 104-105 and 121-128) was *prima facie* obvious to make and use the invention at the time it was made.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be

calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is (703) 306-3483. The examiner can normally be reached from 9:00 a.m. to 5:30 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 703-308-2923. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is (703) 306-3483. The examiner can normally be reached from 9:00 a.m. to 5:30 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 703-308-2923. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

SWL

Samuel Wei Liu, Ph.D.

October 14, 2003

Karen Cochrane Carlson PhD

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER